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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,873	09/05/2003	Shyam S. Mohapatra	USF-182XC1	6872
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SALIWANCHIK LLOYD & SALIWANCHIK A PROFESSIONAL ASSOCIATION PO BOX 142950 GAINESVILLE, FL 32614-2950			LIETO, LOUIS D	
			ART UNIT	PAPER NUMBER
			1632	

DATE MAILED: 01/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/655,873

Applicant(s)

MOHAPATRA ET AL.

Examiner

Louis D Lieto

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 November 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-42 is/are pending in the application.
- 4a) Of the above claim(s) 16,17,32,33 and 40-42 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-15,18-31 and 34-39 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's response to the Restriction was received on 11/19/2004. Claims 1-42 are pending in the instant application. Applicants elected Group V, claims 2-39 and carbohydrate as the single disclosed species, with traverse. Claims 16, 17, 32, 33 and 40-42 are withdrawn by the examiner from further consideration pursuant to 37 CFR 1.142(b). Claims 1-15, 18-31 and 34-39 are currently under examination. It is noted that the claims have not been amended to reflect the elected subject matter. Applicant is reminded that the claims have only been examined to the extent that they read on the elected subject matter.

Election with Traverse

Applicant's election with traverse of Group V, claims 2-39, and carbohydrate as the single disclosed species in the reply filed on 11/19/2004 is acknowledged. Applicant did not make any arguments; therefore applicant's election with traverse has not been found persuasive in overcoming the grounds of restriction. The requirement is still deemed proper and is therefore made FINAL.

Priority

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). Specifically, applicant must include a reference to provisional Application No. 60/319,523 in the beginning of the specification.

Specification

The disclosure is objected to because of the following informalities: SEQ: ID NO: 9 in the brief description of sequences is described as the sequence of the human IL-12 p49 subunit. Such a subunit is not known to exist in the art. The designation of the sequence should be changed to indicate the correct name of the sequence.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15, 18-31 and 34-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1-15, 18-31 and 34-39 are drawn to any method of modulating an immune response comprising administering a nucleic acid sequence encoding IL-12 and IFN- γ , or biologically active fragments or homologs. The claims are drawn to a genus of a nucleic acid sequences that are defined solely by the ability to modulate an immune response to an antigen.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The claimed genus contemplated in the

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specification includes all homologs with greater than 20% sequence identity and fragments at least 8 nucleotides long (Specification pgs. 18-19). This encompasses a nucleotide sequence that encodes a peptide without any amino acid homology to IL-12 or IFN- γ , as long as the peptide modulates an immune response to an antigen. However, since the immune response and its increase or decrease is undefined in the specification a staggering number of nucleic acid molecules are encompassed by this genus.

The factors to be considered when assessing possession of the claimed invention include disclosure of complete or partial structure, physical and/ or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is the requirement that the nucleic acid sequence to be administered modulate an immune response. The specification does not contemplate any specific biologically active fragments or homologs of IFN- γ . The specification only describes the full-length wild type p35 subunit and the full-length wild type p40 subunit of IL-12. Further the specification fails to identify any structural feature or functional element, common to all biologically active fragments or homologs of IL-12 and IFN- γ that are necessary to modulate an immune response in a patient. The specification does not describe what specific amino acid sequence(s) or tertiary structural element(s) is/are required in order for a biologically active fragment or homolog of IL-12 and IFN- γ to modulate an immune response in a patient. While the specification attempts to define the biologically active fragments or homologs by their ability to modulate an immune response, this is a requirement of the invention and not a distinguishing characteristic. Accordingly, in the absence of sufficient recitation of a distinguishing identifying characteristic, the specification does not provide

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adequate written description of the claimed genus of any method of administering a nucleic acid sequence encoding IL-12 and IFN- γ , or biologically active fragments or homologs to modulate an immune response in a patient in need.

The Revised Interim Guidelines state, "when there is substantial variation with the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436, or the Revised Interim Guidelines for Written Description). Case law concurs, stating, "simply describing large genus of compounds is not sufficient to satisfy written description requirement as to particular species or sub-genus" *Fujikawa v. Wattanasin*, 39 USPQ2d 1895 (CA FC 1996). Furthermore, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). Thus, the specification does not meet the written description provision of 35 U.S.C. 112, first paragraph, for a method of administering any nucleic acid encoding biologically active fragments or homologs of IL-12 and IFN- γ , other than administration of plasmids encoding IL-12 and IFN- γ . Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

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Claims 1-15, 18-31 and 34-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting IgE production, increasing IgG2a production, producing more Th-1 like cytokines, and less Th2 like cytokines by administering separate plasmids encoding IL-12 and IFN- γ , each operably linked to a CMV promoter to a patient, does not reasonably provide enablement for a method of modulating any immune response comprising administering any single nucleic acid sequence encoding IL-12 and IFN- γ , or biologically active fragments or homologs thereof; and any operably-linked promoter; to a patient in need. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification does not teach how to modulate any immune response by administering nucleic acids encoding IL-12 and IFN- γ to a patient in need. The term immune responses encompasses a vast array of reactions from the different components of the immune system, such as mast cell degranulation, B cell antibody production, CTL cytotoxicity, macrophage engulfment. The specification does not teach that administration of nucleic acids encoding IL-12 and IFN- γ can increase or decrease any of these immune responses. The working examples only disclose that administration of nucleic acids encoding IL-12 and IFN- γ to mice reduces serum IgE levels, increases IgG2a levels, increases TH-1 like cytokine levels and decreases TH-2 like cytokine levels. Further, figure 2A of the specification shows that the levels of IgG1 show no statistically significant change in mice after administration of nucleic acids encoding IL-12 and IFN- γ . Thus, applicant's data indicates that administration of nucleic acids encoding IL-12 and IFN- γ does not predictably modulate any and all immune responses.

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The specification does not provide enablement on how to use a single nucleic acid molecule encoding any biologically active fragments or homologs of IL-12 or IFN- γ . The working examples only teach the separate construction of a plasmid encoding the p35 and p40 subunit of IL-12 and a plasmid encoding IFN- γ . The specification does not teach or contemplate the construction of a single nucleic acid encoding both IL-12 and IFN- γ , or biologically active fragments or homologs thereof. Further the working examples only describe the use of plasmids that separately encode IL-12 or IFN- γ . A pcDNA3.1 plasmid that contained SEQ ID Nos: 7, 9 and 11 would be over 10kb long. Kreiss et al. teaches that transfection efficiency of plasmids greater than 10kb into primary cells, such as aortic smooth muscle cells plummets for as the plasmid length reaches 10kb {Kreiss et al. (1999) Nucleic Acids Research 27:3792-3798}. In addition, the specification fails to teach that any homolog of IL-12 or IFN- γ can induce an immune response. The claims encompass an enormous number of nucleic acid molecules that could encode biologically active fragment or homolog of IL-12 or IFN- γ . However the specification only teaches the use of SEQ ID Nos: 7, 9 and 11.

The specification also does not provide an enabling disclosure for using any expression vector/promoter combination to express IL-12 and IFN- γ *in vivo*. The claims read on any and all vectors, including plasmids, viral vectors, retroviral vectors, naked DNA and naked RNA. The claims also read on any and all promoters, including SV40, CMV, or SV2. Further, the working examples teach the construction and administration of two pcDNA3.1 plasmids, which separately encode IL-12 and IFN- γ . The language of the claims read on a single nucleic acid sequence. The specification does not teach the administration of a single nucleic acid sequence that encodes both IL-12 and IFN- γ .

Verma et al. states that, the Achilles heel of gene therapy is gene delivery, and that, most of the approaches suffer from poor efficiency of delivery and transient expression of the gene {Verma et al. (1997) Nature, Vol. 389, page 239, column 3, paragraph 2}. Marshall concurs, stating that, difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field, and that, many problems must be solved before gene therapy will be useful for more than the rare application {Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1}. Orkin et al. further states in a report to the NIH that, none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated, and that, while the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol {Orkin et al. (1995) Report and recommendations of the panel to assess the NIH investment in research on gene therapy, page 1, paragraph 3, and page 8, paragraph 2}. Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, and the need for appropriate vector/promoter combinations for a particular cell type. In regards to the latter issue, Verma states that, the search for such combinations is a case of trial and error for a given cell type {Verma, (1997) Nature, 389, page 240}. Thus, given the lack of guidance in the specification on how to modulate any immune response with any single nucleic acid sequence containing any promoter operably linked to a sequence comprising IL-12 and IFN- γ , a skilled artisan would be unable to practice the invention, except as a method for inhibiting IgE production, increasing IgG2a production,

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producing more Th-1 like cytokines and less Th2 cytokines by administering two separate plasmids encoding IL-12 and IFN- γ , in a patient, without arduous and extensive experimentation.

Claims 14, 15 and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting IgE production, increasing IgG2a production, producing more Th-1 like cytokines, and less Th2 like cytokines by administering separate plasmids encoding IL-12 and IFN- γ , and operably linked to a CMV promoter and KBG allergen extract, to a patient, does not reasonably provide enablement for a method of modulating any immune response comprising administering any nucleic acid sequence encoding IL-12 and IFN- γ , or biologically active fragments or homologs thereof; and any operably-linked promoter and any carbohydrate; to a patient in need. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification only teaches the administration of a rough KBG allergen extract to mice prior to or in conjunction with administration of plasmid encoded IL-12 and IFN- γ . The specification does not teach the administration of any isolated carbohydrate to mouse in order to induce an allergic response. The working examples only describe the administration of crude KBG extracts, which contain plant protein, nucleic acids and carbohydrates. This makes it impossible to determine which component is inducing the allergic response. Further not all carbohydrates are capable of inducing an immune response. Park et al. teaches that administration of a disaccharide isolated from a plant can inhibit histamine release and allergic response in rats (Park et al. (2004) *Phytotherapy Research* 18:658-662; Abstract; pg. 660, Figure

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3). Therefore it is impossible to predict that any and all carbohydrates will induce an allergic response when administered to a patient. Thus, given the lack of guidance in the specification on how to modulate any immune response with any nucleic acid sequence containing any promoter operably linked to a sequence comprising IL-12 and IFN- γ , and the art taught unpredictability that any carbohydrate can induce an allergic response, a skilled artisan would be unable to practice the invention, except as a method for inhibiting IgE production, increasing IgG2a production, producing more Th-1 like cytokines and less Th2 cytokines by administering two separate plasmids encoding IL-12 and IFN- γ , and a KBG extract, in a patient, without arduous and extensive experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15, 18-31 and 34-39 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because the phrase “modulating an immune response” is vague. The body of the claim does not make it clear what “modulating an immune response” means. Further, it is unclear what immune response is to be modulated and whether that modulation results in a consistent increase or decrease of the immune response. The phrase immune response encompasses a vast array of reactions from cells such as NK cells, mast cells, macrophages, and eosinophils, as well as humoral components such as antibodies, complement and soluble transferrin. It is unclear from the claim language, which immune response of these components is to be modulated, and if so modulated, whether the result is an increase or decrease in activity.

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Therefore the metes and bounds of the claims cannot be determined. Claims 2-19 depend on claim 1.

Claims 1-15, 18-31 and 34-39 are indefinite because the term “biologically active fragments” is vague. The body of the claim does not make clear what “biologically active fragments” means. The specification defines “biologically active fragments” in terms of modulating an immune response. However since it is unclear what is to be modulated, see above, the metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-10, 12-14, 20-29, 34-36, 38, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. {Hogan et al. (1998) Eur. J. Immunol. 28: 413-423}, and further in view of Li et al. {Li. et al. (1996) J. Immunol. 157: 3216-3219} and Carroll et al. {Carroll et al. (1998) J. of the Nat. Canc. Inst. 90:1881-1887}.

Hogan et al teaches the construction and administration of a vaccinia virus encoding the p35 subunit and the p40 subunit of mouse IL-12 operably linked to a promoter (pg. 420, Section 4.7). Said sequences are biologically equivalent to SEQ ID NOs: 7 & 8 (human p35 subunit) and SEQ ID Nos: 9 & 10 (human p40 subunit). Further, Hogan teaches that in mice sensitized with OVA (pg. 420, Section 4.2), IL-12 gene delivery inhibits airway inflammation (pg. 415, Figure

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1, Col. 1), increases the levels of IFN- γ and decreases the levels of IL-4 and IL-5 expressed in lung cells (pg. 416, Figure 2) after administration in gelatin saline (pg. 420, Section 4.7). Hogan et al. teaches that IL-12 protects against lung damage by increasing the levels of IFN- γ expressed (pg. 418, col.1). Finally, Hogan et al teaches that viral titers in the mouse lung peaked at day 3 after administration of vaccinia encoded IL-12 (pg. 417, Figure 4), which indicates that the viral nucleic acid was contained within a cell. Hogan et al. does not teach the administration of IFN- γ encoded within the same vaccinia virus.

Li et al. supplements Hogan et al. by providing guidance on the construction of a vector encoding IFN- γ and operably linked to a promoter; followed by administration of the vector to mice suspended in lipofectamine (pg. 3216, Col. 1, Materials and Methods). Said plasmid encoded IFN- γ is biologically equivalent to SEQ ID NOs: 11 & 12 (human IFN- γ). Li et al. shows that the IFN- γ is expressed in higher levels of treated mice and that the vector is contained within mouse lung cells (pg. 3217, Figure 1). Finally, Li et al shows that administration of vector encoded IFN- γ inhibits pulmonary allergic responses in mice sensitized with CA (pg. 3217 col. 1) and leads to a significant decrease in eosinophilia (pg. 3218, Figure 2, Col 2.).

Carroll et al. supplements Hogan et al. by providing guidance on the construction of a vaccinia virus that express IL-12 and an additional immunostimulatory molecule (Abstract, pg. 1882, col. 1, Materials and Methods). Carroll et al. teaches that the “vaccinia virus is well-characterized expression vector that has been used to express a wide variety of recombinant proteins” (1881, col. 1).

Based on the guidance provided by Hogan et al. on a method of administering vaccinia virus encoded IL-12 to mice sensitized with antigen to reduce allergic lung inflammation and the

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teachings of Li et al. on a method of administering plasmid encoded IFN- γ to mice sensitized with antigen to reduce allergic lung inflammation and the teachings of Carroll et al. that vaccinia viruses can be used to encode multiple immunostimulatory proteins, it would be *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Hogan et al. with the guidance of Li et al. by constructing a vaccinia viral vector that encoded both IL-12 and IFN- γ . A practitioner in the art would be motivated to construct a single vector encoding both IL-12 and IFN- γ in order to increase serum IFN- γ levels above those produced by vector encoded IFN- γ or IL-12 alone thereby decreasing the eosinophils and IL-4 and IL-5 and producing better protection against allergic lung inflammation.

The person of ordinary skill in the art would have a reasonable expectation of success because the construction of a vaccinia virus encoding IL-12 and IFN- γ comprises a minor modification to the methods taught by Hogan et al.

Please note, that the further prior art is exemplified by Kumar et al., who teaches the administration of separate IL-12 and IFN- γ plasmid DNAs as vaccine adjuvant with KBG in a mouse model {Kumar et al. (2001) J. Allergy Clin Immunol; 108:402-8}.

Claims 11, 15, 19, 30, 31 and 37 are free of the prior art of record.

No claims are allowed.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Amy J Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Dr. Louis D. Lieto
Patent Examiner
Art Unit 1632

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER

